

A METHOD OF PREVENTING OR TREATING GLAUCOMA

This application claims priority from U.S. Provisional Application No. 60/524,912, filed November 26, 2003, the entire content of which is
5 incor herein by reference.

TECHNICAL FIELD

The present invention relates, in general, to glaucoma and, in particular, to a method of preventing or treating glaucoma using statins.

10

BACKGROUND

Glaucoma is one of the three leading causes of blindness in the United States and it is a leading cause of blindness in the world. Over 2.2 million people in the United States have glaucoma, and
15 several million more are at risk of developing the disease. As the population ages, the number of individuals with glaucoma will continue to grow since glaucoma affects the oldest individuals disproportionately.

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Glaucoma is not just one disease, rather, it is a spectrum of conditions that share a final common pathway of acquired, progressive deterioration of the neuronal components of the optic nerve. Neuronal death results in loss of vision once a
25 sufficient number of individual nerves are destroyed.

Factors associated with the development of glaucoma and its progression have been identified and are in the process of being clarified. Elevated intraocular pressure (IOP) is the leading cause of glaucoma. Pressure is elevated because drainage of aqueous fluid from within the eye is impaired. Current treatments for glaucoma center on reducing pressure in the eye by reducing the amount of aqueous fluid being produced or by enhancing the flow of fluid out of the eye by mechanical or other means. Currently available drugs do not enhance or restore functioning of the natural drainage pathway.

Glaucoma patients may also suffer reduced blood flow to the optic nerve and neuronal tissue, diminished resistance of the nerve tissue to damage, and compliance of connective tissue surrounding and supporting the optic nerve. Current treatments do not address any such factors. Only one agent, Memantine, is in phase III clinical trials (Allergan) as an agent that may increase the relative resistance of the nerve tissue to damage (i.e., neuroprotective).

The use of statins has been associated in some studies with a diminished risk of developing age-related macular degeneration as well as a potential for reducing the risk for several medical conditions related to cardiovascular disease (Hall et al, BMJ 323:375-376 (2001), McCarty et al, MJA 175:340 (2001), Shovman et al, Immunol. Res. 25:271-285 (2002), Kagansky et al, QJM 94:457-463 (2001)). The presumed direct causal mechanisms have centered on

the effect of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors in reducing cholesterol production and enhancing LDL-cholesterol removal from plasma. To the extent that excess
5 total cholesterol or LDL cholesterol is implicated in these conditions, use of the statins would reduce the risk of developing, or at least delay the onset of, these conditions. Statins also inhibit non-steroidal isoprenoid production (Edwards and
10 Ericsson, *Annu. Rev. Biochem.* 68:157-185 (1999), Comparato et al, *Nutr. Metab. Cardiovasc. Dis.* 11:328-343 (2001), Takemoto and Liao, *Arterioscler. Throm. Vasc. Biol.* 21:1712-1719 (2001)). Many statins also inhibit the activity of rho-kinase,
15 such inhibition has been shown to enhance aqueous outflow (Rao et al, *Invest. Ophthalmol. & Vis. Sci.* 42:1029-1037 (2001)). There may, of course, be as yet undiscovered or indirect effects of these compounds that would help explain their protective
20 associations.

The present invention provides a new approach to the field of therapeutics for patients with glaucoma. Provided is a method of preventing or treating glaucoma using statins.

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SUMMARY OF THE INVENTION

The present invention relates generally to glaucoma. More specifically, the invention relates to a method of preventing glaucoma or reducing the

risk of glaucoma development using statins. The invention also relates to a method of treating glaucoma using statins.

Objects and advantages of the present invention
5 will be clear from the description that follows.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. Significant trend towards a reduced risk of glaucoma with longer statin use.

DETAILED DESCRIPTION OF THE INVENTION

10 The present invention relates to the use of statins to reduce the risk of glaucoma development in a patient. The invention further relates to a method of treating glaucoma or inhibiting progression of the disease.

15 The term statin refers to compounds that inhibit the transformation of hydroxymethylglutaryl-coenzyme A (HMG-CoA) to mevalonic acid as catalyzed by the enzyme HMG-CoA reductase. Compounds capable of effecting such inhibition can be identified
20 readily by one skilled in the art using standard assays (see, for example, Methods of Enzymology 71:455-509 (1981) and references cited therein).

Examples of statins suitable for use in the present invention include the natural fermentation
25 products, mevastatin and lovastatin, as well as semi-synthetic and totally synthetic statins described, for example, in USPs 3,983,140,

4,231,938, 4,346,227, 4,444,784, 4,450,171,
4,681,893, 4,739,073, 5,177,080, 5,273,995,
5,284,953, 5,354,772, 5,356,896, and 5,856,336, and
in European Patent Application Nos. 738,510 A2 and
5 363,934 A1 and EP 491,226. Additional examples of
HMG-CoA reductase inhibitors suitable for use in the
invention are described in Yalpani, "Cholesterol
Lowering Drugs", Chemistry & Industry, pp. 85-89
(1996).

10 Preferably, the statin used in the present
method is mevastatin, lovastatin, pravastatin,
velostatin, simvastatin, fluvastatin, cerivastatin
(rivastatin), dalvastatin, fluindostatin or
atorvastatin, or a prodrug thereof, or a
15 pharmaceutically acceptable salt of such statin or
prodrug. More preferably, the statin is lovastatin
(MEVACOR (USP 4,231,938)), simvastatin (ZOCOR (see
USP 4,444,784)), pravastatin (PRAVACHOL (see
USP 4,346,227)), fluvastatin (LESCOL
20 (USP 5,354,772)), atorvastatin (LIPITOR
(USP 5,273,995)), cerivastatin (USP 5,177,080)) or
nivastatin (NK-104 (USP 5,284,953, 5,356,896 and
5,856,336)).

Methods of producing suitable statins are
25 described, for example, in one or more of the above
cited patents/patent applications.

Statins suitable for use in the invention can
be formulated into pharmaceutical compositions, for
example, as described in the above-referenced
30 patents/applications. The statin is preferably
formulated in a form suitable for oral

administration, for example, as a tablet or capsule. Optimum dosing regimens can be established by one skilled in the art without undue experimentation. While dosing regimens used for glaucoma treatment/prevention can be the same as regimens used for lowering cholesterol, optimum regimens can be readily established by one skilled in the art.

Combination therapy can also be used in the methods of the present invention. That is, a selected statin can be used in combination with another medicament(s) known to be useful for the treatment of glaucoma. Examples of agents that can be used in combination with statins in the present invention include β -adrenergic blocking agents, carbonic anhydrase inhibitors, miotics, sympathomimetics and prostaglandin agonists. Specific examples of currently available medicaments suitable for use in combination with statins include Latanoprost (Xalatan), Bimatoprost (Lumigan), Travoprost (Travatan), and Unoprostone (Rescula). A selective EP₄ receptor agonist or prodrug thereof as described in U.S. Patent Application 20030207925 may or may not be used in combination with statins in the present methods. Most medicaments presently used for glaucoma treatment are administered as droplets to the eye. Statins can also be administered as droplets to the eye but have the advantage of being administerable orally as well. Therefore, when combination therapy is used, the dosage forms can be the same or they can differ

(e.g., the statin may be present in a form suitable for oral administration while the other medicament may be present as eye droplets (or they can both be administered as droplets to the eye)). The
5 compounds can be administered at essentially the same time or at different times.

It will be appreciated from the present disclosure that the present methods have application in the human therapeutic strategies and in
10 veterinary settings as well.

With a greater understanding of the multiple mechanisms that could potentially impact the outflow system or the optic nerve in glaucoma, there are plausible means by which statin use could be
15 associated with a reduced risk of developing glaucoma. While not wishing to be bound by theory, it is noted that by reducing atherosclerotic processes and subsequent vascular diseases, statins may directly protect optic nerve head vasculature or
20 may indirectly improve ocular blood flow. Since the trabecular meshwork has endothelial cells that share many attributes of vascular endothelial cells, statins may also exert a protective effect in enhancing trabecular endothelial cell function.
25 Additionally, many statins also inhibit the activity of rho-kinase, such inhibition has been shown to result in an increase in aqueous outflow.

Certain aspects of the invention can be described in greater detail in the non-limiting
30 Examples that follows.

EXAMPLE 1

Experimental Details*Study population and data source*

The Birmingham (Alabama) Department of Veterans
5 Affairs Medical Center (BVAMC) is 134-bed acute
tertiary care medical facility and serves as a
Veterans Hospital Administration tertiary care
referral center for Alabama. All patients who had
at least one visit (inpatient or outpatient) at the
10 Birmingham BVAMC between a specified period were
eligible for study inclusion. Because the
prevalence of glaucoma is low below age 50, the
study population was limited to patients 50 and
older. Females were also excluded as they
15 represented such a small proportion of the patient
population (10.8%) that meaningful analyses were
impossible.

The BVAMC provided data files containing
demographic information (age, gender, race) and
20 clinical and medication information for each
patient. The clinical file contained a description
of each diagnosis made at the BVAMC during inpatient
and outpatient visits and the diagnosis date. All
diagnoses were coded using the International
25 Classification of Diseases, Ninth Revision, Clinical
Modification (ICD-9CM). The medication file
contained information on each medication prescribed
during each patient visit. This file also contained
the prescription date and the date the prescription

was filled. For both the clinical and medication files, the information provided pertained to all diagnoses and medications over the course of each patient's history with the BVAMC and not just those
5 that occurred in the specified time period.

Study Design

Within the study population, a nested case-control study was conducted. Cases of glaucoma were defined using the ICD-9CM codes 365.1 (open-angle
10 glaucoma), 365.8 (other specified forms of glaucoma) and 365.9 (unspecified glaucoma). It was believed that the use of the non-specified forms of glaucoma were likely to reflect open-angle glaucoma that was imprecisely coded. To the extent that they truly
15 represent other forms of glaucoma that are not associated with statin use, the bias so introduced would be towards the null.

Information on the glaucoma diagnosis date was procured and is referred to below as the index date.
20 Because this study addressed the association between statin use and the new diagnosis of glaucoma, patients who had a glaucoma diagnosis prior to the observation period of the study (prevalent cases) were excluded.

25 Controls were randomly selected from the study population who did not have a glaucoma diagnosis by the end of the observation period. To be considered an eligible control for a given case, the control must have had an encounter with the BVAMC (inpatient
30 or outpatient) on or before the index date of the

matched case. Ten controls were selected for each case and matched on age (± 1 -year). Each control was assigned the index date associated with their matched case.

5 The prescription file was queried for the presence of filled statin (atorvastatin, cerivastatin, fluvastatin, pravastatin, simvastatin, lovastatin) prescriptions. Non-statin lipid-lowering agents (e.g., fibrates, nicotinic acid)
10 were also extracted from the prescription file. Only those prescriptions that were filled prior to the index date for each matched set of cases and controls were considered. Time since first statin use was calculated as the time between the first
15 statin prescription and the index date. Statin users, were also classified as being current or past users with the former being those who had a statin prescription filled within 6 months before the index date and the latter being those whose last
20 prescription fill date was greater than 6 months before the index date. An analogous set of variables was created for the non-statin lipid-lowering agents.

 Information on the presence of the following
25 conditions was extracted from the clinical data file: ischemic heart disease (ICD-9CM codes 410 though 414), cerebrovascular disease (ICD-9CM codes 430 though 438), lipid metabolism disorders (ICD-9CM code 272), hypertension (ICD-9CM codes 401 though
30 405), diseases of the arteries, arterioles and capillaries (ICD-9CM codes 440 though 448), and

diabetes (ICD-9CM code 250). For the purposes of analysis, only those diagnoses that were recorded prior to the index date were considered.

Statistical analysis

5 Conditional logistic regression was used to calculate an odds ratio (OR) and 95% confidence interval (CI) for the association between any statin use and the risk of developing glaucoma. ORs and 95% CIs were also estimated for current and past
10 statin users relative to non-users and according to time since first prescription. A similar set of analyses was conducted for non-statin lipid-lowering agents. Stratified analyses were conducted to determine if diabetes, lipid metabolism disorders,
15 hypertension, cardiovascular disease, cerebrovascular disease, and arterial disease modified the association between statin use and glaucoma. There were an insufficient number of patients using non-statin lipid-lowering agents to
20 conduct a similar set of stratified analyses.

Results

Table 1 presents the demographic and medical characteristics among the glaucoma cases and control. By design, the mean age of both cases and
25 controls was equivalent. There were twice as many African-Americans among the cases compared to controls. Those with glaucoma were more likely to also have diabetes, lipid metabolism disorders, and hypertension.

Table 2 demonstrates the statin and non-statin medication use characteristics among glaucoma cases and non-glaucoma controls, as well as the unadjusted and adjusted ORs. While cases were more likely to
5 have filled a statin prescription (OR 1.23, 95% CI 0.99 to 1.51), following adjustment for diabetes, lipid metabolism disorders, hypertension, cardiovascular disease, cerebrovascular disease, and arterial disease, a protective association was
10 observed (OR 0.85, 95% CI 0.66 to 1.09), albeit not statistically significant. This association was observed, albeit not significantly, for past (OR 0.74, 95% CI 0.53 to 1.04) but not current (OR 0.94, 95% CI 0.70 to 1.27) statin use. There was a
15 significant trend towards a reduced risk of glaucoma with longer term statin use ($p=0.04$) (Figure 1). Indeed, use of statins for greater than 23 months was associated with a statistically significant reduction in the risk of glaucoma (OR 0.60, 95%
20 CI 0.39 to 0.92).

Use of non-statin lipid lowering medications was also associated with a significantly reduced risk of glaucoma (OR 0.59, 95% CI 0.37 to 0.97) that was also apparent among both current and past users
25 although neither association was statistically significant. However, this association was limited to those with <12 months of use (OR 0.38, 95% CI 0.18 to 0.79). When considering the joint effect of statin and non-statin medications, the largest risk
30 reduction was associated with use of both types of medications (OR 0.52) followed by non-statin use

only (OR 0.60) and statin use only (OR 0.86).
However, none of these associations was
statistically significant.

Table 3 presents ORs and 95% CIs for the
5 association between statin use and glaucoma
stratified according to the presence of
comorbidities. Once the other medical
characteristics are controlled for, significant
associations between statin use and glaucoma were
10 observed among those with lipid metabolism
disorders, cardiovascular disease, and those without
cerebrovascular disease.

Conclusions

The results of this analysis demonstrate a
15 significant and meaningful trend towards reduced
risk of glaucoma development with longer-term statin
use, particularly two or more years. Evaluating
larger datasets with longer follow-up periods, such
as those with managed care companies or with
20 insurance company claims files where both disease
and pharmacy data are maintained, would allow a more
definitive evaluation of the usefulness of statins
as an additional therapy for glaucoma or its
prevention.

25 Such an endeavor is clearly worthwhile, based
not only on the results of the current study but
also on some plausible potential mechanisms whereby
such a protective effect might occur. First, many
statins inhibit the activity of rho-kinase; such
30 inhibition has been shown to enhance aqueous

outflow, thereby presumably lowering IOP (Rao et al, Invest. Ophthalmol. & Vis. Sci. 42:1029-1037 (2001)). It would be interesting to examine the effect of statin use on the level of IOP, controlling for the status of glaucoma and the intensity of treatment. Second, the ability of statins to reduce cardiovascular disease may directly or indirectly protect the vascular supply to the optic nerve or eye. Interestingly, statin use is associated with a higher, albeit not statistically meaningful, elevation of risk of glaucoma among those with cerebrovascular disease compared to a lower risk among those with cardiovascular disease. This may indicate that the direct and indirect mechanisms have opposing effects or that there are additional factors at work.

If the trend and the magnitude of the effect seen with statin use of greater than 23 months is upheld with larger sample sizes in future studies, the protective effect is substantial and of similar magnitude to the benefit of lowering IOP through the use of medications in the OHTS study and of other treatments in other studies (Kass et al, Arch. Ophthalmol. 120:701-713 (2002), Collaborative Normal Tension Study Group Am. J. Ophthalmol. 126:487-497 (1998)). This would also imply that a new therapeutic class of agents might be effective for the care and treatment of glaucoma patients.

The side effects of statins on ocular structures have been studied to a limited degree. While animal models might indicate a higher risk of

cataract development due to the rho-kinase inhibition of statins, human studies have demonstrated no elevated risk of cataracts among those taking statins (Schlienger et al, Arch. Intern. Med. 161:2021-2026 (2001), Laties et al, Am. J. Cardiology 67:447-453 (1991)). Obviously, longer-term follow-up over many years will be needed to be able to conclude that such chronic use is completely safe for the eye. In addition, the potential systemic side effects of statins need to be carefully considered.

The intriguing finding of some protective association with non-statin use also raises the possibility that lipid diseases as a whole may be associated with the presence of glaucoma, as seen in the higher proportion of cases with lipid disorders compared to controls. There have been no studies to suggest this is the case in population-based evaluations to date. Nevertheless, the associations found here, both in the protective association with cholesterol lowering agents and the higher rate of lipid disorders seen in those with glaucoma compared to controls, suggests that such inquiry is warranted. Thus, additional work is also needed to clarify the nature of the association between the presence of lipid disorders and the use of medications to lower lipid.

The evidence in favor of an independent role for treatment, however, is found in the significant OR of 0.63 among those with lipid disorders who have

received statin treatment compared to those who have not, even after adjusting for co-morbid conditions.

Among those without cerebrovascular disease, statin use was protective for the development of
5 glaucoma (OR of 0.76, with a CI of 0.58 to 0.99) while those with cerebrovascular disease demonstrated a positive association between statin use and glaucoma (OR of 2.01, with a CI of 0.99 to 4.10). This result is difficult to interpret. This
10 could be a spurious association or an anomaly in the data or results. Alternatively, it may reflect the more general state of vascular supply to the central nervous system. Those without a history of cerebrovascular disease have a statin association
15 similar to the other subpopulations and the population as a whole in this study. Those with a history may reflect a strong difficulty in vascular flow that overrides the effects of statins, since even those who do not use statins have an elevated,
20 albeit not significant, risk of glaucoma (OR of 1.65). Further, those who have such conditions and who have been placed on statins may have cerebrovascular disease of greater severity than those that do not.

25 The above study has certain limitations. First, the study population consisted entirely of men, since it was an older VA population. Additional research on the association between statin use and glaucoma among women is necessary.
30 Second, the diagnoses of glaucoma were made by individual physicians without the use of

standardized criteria, which could introduce significant differences relative to other studies and study populations. However, there is no reason to expect the diagnosis of glaucoma to have been
5 biased by the use of statins. Third, the diagnoses were subject to miscoding into ICD-9 codes; again, however, there is no reason to suspect that bias would result from this. Fourth, no clinical data was available, so no comment can be made on the
10 severity of glaucoma. Fifth, statin use was defined on the basis of a filled prescription within the BVAMC pharmacy service. This suggests that a patient with a statin prescription record but no matching fill record would be classified as a non-
15 statin user even though he did indeed use statins by filling the prescription outside the BVAMC system. Such misclassification, however, would only bias to the null. Additionally, since over 90% of statin prescriptions were filled at the BVAMC, this is
20 unlikely to have produced a significant effect. Finally, race was unknown for a large proportion of our study population (both cases and controls). However, the race distribution among those with known data was similar to what would be expected
25 given population-based studies and thus unlikely to introduce spurious results in the analyses. Information on additional potentially confounding characteristics (e.g., smoking) was similarly not available.

30 An important methodological issue is the possibility of "left-censoring" in that many

patients with pre-existing glaucoma would have been captured in the first year or two of the study, since case identification was made on the basis of the first visit at which an open-angle or
5 unspecified type of glaucoma was diagnosed. Thus, it was expected that many of the "new diagnosis" cases of glaucoma were actually prevalent cases that were first seen at the BVAMC and recorded into the database and captured by the selection algorithm as
10 a "new diagnosis" case due to the enrollment time intervals. This issue, however, is unlikely to detract from the findings noted here because there is no a priori reason to believe that prevalent cases would differ from incident cases for statin or
15 other anti-lipid agents use.

EXAMPLE 2

Trabecular meshwork (TM) and ciliary muscle cells possess smooth muscle-like properties that have
20 been hypothesized to be involved in the regulation of aqueous outflow facility. The purpose of the following study was to investigate the effects of cholesterol lowering statin drugs, which are known to influence the Rho pathway, on cell shape,
25 contractile properties, cytoskeletal integrity in TM and ciliary muscle cells, and aqueous outflow through the TM.

Experimental Details

Porcine primary trabecular meshwork (PTM) and ciliary muscle cells (PCM) were cultured and treated with lovastatin or compactin at concentrations of 25
5 μM and 50 μM . Effects on actin stress fibers (phalloidin staining) and focal adhesion formation (vinculin) were evaluated by immunofluorescence staining. Urea/glycerol polyacrylamide gel electrophoresis and Western blot analysis were
10 utilized to investigate the effects of statins on myosin light chain (MLC) phosphorylation. Changes in cell shape were recorded using the phase contrast microscope. A constant flow organ culture perfusion system was used to measure outflow facility in
15 perfused porcine eye anterior segments.

Results

PTM cells treated with lovastatin and compactin demonstrated dramatic changes in cell shape, with cells becoming rounded and separated from each other.
20 These morphological changes were found to be reversible upon drug withdrawal. Within 24 hours of drug administration, there was evidence of actin depolymerization and loss of focal adhesions. Supplementation of cell culture media containing
25 lovastatin with geranylgeranyl pyrophosphate completely reversed the changes in cell shape and cytoskeletal organization. Lovastatin and compactin also induced marked reduction in MLC phosphorylation indicative of cellular relaxation. Similar changes

in cell shape, cytoskeletal organization and MLC phosphorylation were observed in PCM cells treated with statins. In an ongoing study, perfusion of porcine eye anterior chambers with 100 μ M lovastatin
5 caused a 48% drop in intraocular pressure at 72 hours, as compared to a 22% reduction in IOP in control eyes.

Conclusions

These data demonstrate that statins (e.g.,
10 lovastatin and compactin) induce cellular relaxation in TM and ciliary muscle cells via effects on cell shape, actin cytoskeletal integrity and MLC phosphorylation. These effects of statins appear to involve the isoprenylation of small GTP-binding
15 proteins such as Rho GTPase. Furthermore, these statins demonstrated the ability to decrease IOP in an organ culture perfusion model indicating their potential use in glaucoma therapy.

* * *

20 All documents and other information sources cited above are hereby incorporated in their entirety by reference.

TABLE 1. Demographic and Medical Characteristics Among Glaucoma Cases and Non-Glaucoma Controls

	Cases (N=667)	Controls (N=6667)	p-value
Demographic Characteristics			
Age (in years), mean	69.0	69.0	.9259
Race, n (%)			.7576
Caucasian	252 (37.8)	3162 (47.4)	
African-American	193 (28.9)	939 (14.1)	
Other	9 (1.4)	26 (0.4)	
Unknown	213 (31.9)	2540 (38.1)	
Medical Characteristics			
Diabetes, n (%)	172 (25.8)	818 (12.3)	<.0001
Lipid metabolism disorders, n (%)	100 (15.0)	545 (8.2)	<.0001
Hypertension, n (%)	341 (51.1)	1811 (27.2)	<.0001
Cardiovascular disease, n (%)	130 (19.5)	1312 (19.7)	.9069
Cerebrovascular disease, n (%)	50 (7.5)	453 (6.8)	.4943
Arterial disease, n (%)	41 (6.2)	368 (5.5)	.5010

TABLE 2. Statin and Non-Statin Medication Use Characteristics Among Glaucoma Cases and Non-Glaucoma Controls and Associated Odds Ratios (ORs) and 95% Confidence Intervals (CIs)

	Cases (N=667)	Controls (N=6667)	OR (95% CI)	OR (95% CI)*
Statin Use Characteristics				
Statin use, n (%)				
No	548 (82.2)	5663 (84.9)	1.00	1.00
Yes	119 (17.8)	1004 (15.1)	1.23 (0.99-1.51)	0.85 (0.66-1.09)
Non use	548 (82.2)	5663 (84.9)	1.00	1.00
Current use	71 (10.6)	535 (8.0)	1.37 (1.06-1.78)	0.94 (0.70-1.27)
Past use	48 (7.2)	469 (7.0)	1.06 (0.78-1.44)	0.74 (0.53-1.04)
Duration of use (in months), n (%)				
Non use	548 (82.2)	5663 (84.9)	1.00	1.00
<12	68 (10.2)	507 (7.6)	1.39 (1.06-1.81)	1.03 (0.77-1.39)
12 - 23	21 (3.2)	191 (2.9)	1.14 (0.72-1.80)	0.75 (0.46-1.23)
>23	30 (4.5)	306 (4.6)	1.01 (0.69-1.49)	0.60 (0.39-0.92)
Non-Statin Cholesterol Lowering Medication Use Characteristics				
Non-statin agent use, n (%)				
No	647 (97.0)	6441 (96.6)	1.00	1.00
Yes	20 (3.0)	226 (3.4)	0.88 (0.55-1.40)	0.59 (0.37-0.97)
Non use	647 (97.0)	6441 (96.6)	1.00	1.00
Current use	8 (1.2)	91 (1.4)	0.88 (0.42-1.81)	0.60 (0.29-1.27)
Past use	12 (1.8)	135 (2.0)	0.89 (0.49-1.61)	0.59 (0.32-1.09)
Duration of use (in months), n (%)				
Non use	647 (97.0)	6441 (96.6)	1.00	1.00
<12	8 (1.2)	138 (2.1)	0.58 (0.28-1.18)	0.38 (0.18-0.79)
=12	12 (1.8)	88 (1.3)	1.36 (0.74-2.50)	0.95 (0.50-1.79)
Statin and Non-statin Use Characteristics				
Neither statin nor non-statin	538 (80.7)	5558 (83.4)	1.00	1.00
Statin use only	109 (16.3)	883 (13.2)	1.28 (1.03-1.59)	0.86 (0.66-1.11)
Non-statin use only	10 (1.5)	105 (1.6)	0.98 (0.51-1.89)	0.60 (0.30-1.18)
Statin and non-statin use	10 (1.5)	121 (1.8)	0.85 (0.45-1.64)	0.52 (0.26-1.04)

* Adjusted for diabetes, lipid metabolism disorders, hypertension, cardiovascular disease, cerebrovascular disease, and arterial disease.

TABLE 3. Odds Ratios (ORs) and 95% Confidence Intervals (CIs) for the Association Between Statin Use and Glaucoma Stratified According to Presence of Medical Conditions

	OR (95% CI)	OR (95% CI)*
Diabetes		
No	1.12 (0.87-1.46)	0.79 (0.58-1.07)
Yes	0.97 (0.67-1.40)	0.97 (0.63-1.50)
Lipid metabolism disorders		
No	1.11 (0.85-1.46)	0.97 (0.73-1.30)
Yes	0.57 (0.37-0.88)	0.63 (0.41-0.99)
Hypertension		
No	1.40 (1.01-1.95)	1.05 (0.72-1.53)
Yes	0.71 (0.54-0.94)	0.75 (0.54-1.03)
Cardiovascular disease		
No	1.59 (1.23-2.06)	0.98 (0.73-1.33)
Yes	0.81 (0.55-1.18)	0.63 (0.42-0.97)
Cerebrovascular disease		
No	1.17 (0.94-1.47)	0.76 (0.58-0.99)
Yes	1.65 (0.89-3.06)	2.01 (0.99-4.10)
Arterial disease		
No	1.26 (1.01-1.57)	0.86 (0.66-1.11)
Yes	0.87 (0.42-1.80)	0.74 (0.32-1.72)

* Adjusted for diabetes, lipid metabolism disorders, hypertension, cardiovascular disease, cerebrovascular disease, and arterial disease where appropriate.